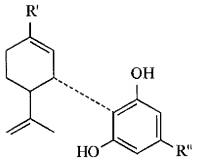


having selective activity in the peripheral, but not in the central nervous system. Use of (+)-CBD derivatives as analgesics, anti-inflammatory and anti-diarrheal agents is also disclosed.

Claim rejections - 35 USC §112

The Examiner rejected claims 5 and 17 for being indefinite. The Examiner holds that the claim does not recite that the compounds are modulators of the peripheral nervous system but not of the central nervous system.

As the Examiner commented, the specification suggests that the compounds are intended to be selective for peripheral cannabinoid receptors, as opposed to CNS cannabinoid receptors, but the claim does not reflect how this notion is met.

Although applicant is of the opinion that the definition "selective peripheral nervous system modulator" is clear from the description, in order to expedite examination claim 5 has been amended to recite: "peripheral nervous system modulator".

Likewise, in view of the Examiner's rejection of claim 17, this claim has also been amended in order to expedite examination.

The Examiner further rejected claim 17 because he maintains that the meaning of "disorder(s) associated with the peripheral cannabinoid system" is unclear. The Examiner stated that the basis for the association with the cannabioid system is lacking, for example, it is unclear whether the claim relies on the condition being a result of a malfunction of the cannabinoid system, or if the condition bears an indirect relationship with the cannabinoid system.

The term "associated with (a disease)" is well known to the person of skill in the art of medicine, and is commonly used. The specification gives several examples of diseases or conditions associated with the peripheral cannabinoid system,

like diarrhea, pain, and others. The specification and examples show specificity of the claimed compounds to the peripheral cannabinoid system, hence applicant is of the opinion that the definition should be acceptable.

Claim rejections - 35 USC §102

The Examiner rejected claims 1, 2, 3, 4, 5 and 17 for lack of novelty under 35 U.S.C. 102(b), in view of US Patent No. 6,630,507 to Hampson et al.

The Examiner maintains that Hampson teaches a pharmaceutical composition that includes cannabinoids having structures as depicted in col. 5, lines 25-67. The Examiner opines that the structure is a finitely small set, and that the man of skill in the art immediately **envisages** a structure such as a compound of Formula (I) in which R' is COOH or CH_2OH and R" is a branched alkyl (as depicted in the Office Action). Applicant respectfully traverses that analysis.

Since the examiner used the phrase "the structure is a finitely small set, and that the man of skill in the art immediately envisages a structure", the examiner's analysis must be based on an erroneous interpretation of *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). The *Petering* standard is still applicable under the current KSR standard, since the USPTO maintained that standard in its updated and current MPEP.

In that decision, it was held that a genus may be so small that, when considered in light of the **totality of the circumstances**, it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would... envisage *each member*" of the genus. More specifically, the court in *Petering* stated:

> A simple calculation will show that, excluding isomerism within certain of the R groups, the limited class we find in Karrer contains only 20 compounds. However, we wish to point out that it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved, including such factors as the limited number of

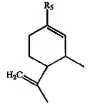
> variations for R, only two alternatives for Y and Z, no alternatives for the other ring positions, and a large unchanging parent structural nucleus. With these circumstances in mind, it is our opinion that Karrer has described to those with ordinary skill in this art each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name. *Id.* (emphasis in original).

There is a significant caveat to *Petering* ruling. That caveat is that Rejection of claimed compound in light of prior art genus based on *Petering* is not appropriate where the prior art does not disclose a **small recognizable class of compounds with common properties**. *In re Ruschig*, 343 F.2d 965, 974, 145 USPQ 274, 282 (CCPA 1965). The USPTO, in MPEP, acknowledges the *In re Ruschig* distinction.

The problem with the examiner's rejection is that the examiner did not review the totality of the circumstances, as required by law, when it reviewed Hampson's disclosures. Hampson's taught more than 7 different genus cannabinoid structures with more than 100 different variations thereof. To illustrate this point, we will provide all the possible cannabinoid structures disclosed by Hampson. Those cannabinoid structures are as follows:

The cannabinoid may be a cannabinoid other than THC, HU-210, or other potent cannabinoid receptor agonists. The cannabinoid may also be other than HU-211 or any other NMDA receptor antagonist that has previously been reported. A potent cannabinoid receptor agonist is one that has an EC_{50} at the cannabinoid receptor of 50 nM or less, but in more particular embodiments 100 nM or 250 nM or less. In disclosed embodiments the cannabinoid is not psychoactive, and is not psychotoxic even at high doses. In some particularly disclosed embodiments, the cannabinoid is selected from the group:

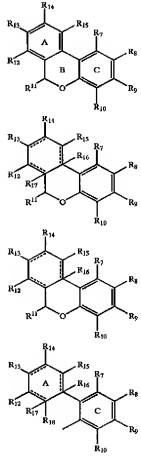
where A is aryl, and particularly



but not a pinene such as:

and the R_1–R_5 groups are each independently selected from the groups of hydrogen, lower substituted or unsubstituted alkyl, substituted or unsubstituted carboxyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alcohol, and substituted or unsubstituted ethers, and R_6–R_7 are H or methyl. In particular embodiments, there are no nitrogens in the rings, and/or no amino substitutions on the rings.

In other embodiments, the cannabinoid is one of the following:



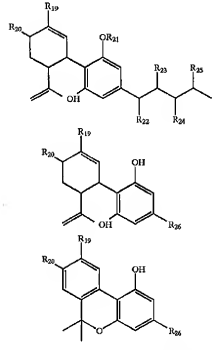
where there can be 0 to 3 double bonds on the A ring, as indicated by the optional double bonds indicated by dashed lines on the A ring. The C ring is aromatic, and the B ring can be a pyran. Particular embodiments are dibenzo pyrans and cyclohexenyl benzenediols. Particular embodiments of the cannabinoids of the present invention may also be highly lipid soluble, and in particular embodiments can be dis-

solved in an aqueous solution only sparingly (for example 10 mg/ml or less). The octanol/water partition ratio at neutral pH in useful embodiments is 5000 or greater, for example 6000 or greater. This high lipid solubility enhances penetration of the drug into the CNS, as reflected by its volume of distribution (V_d) of 1.5 L/kg or more, for example 3.5 L/kg, 7 L/kg, or ideally 10 L/kg or more, for example at least 20 L/kg. Particular embodiments may also be highly water soluble derivatives that are able to penetrate the CNS, for example carboxyl derivatives.

R_{7-18} are independently selected from the group of H, substituted or unsubstituted alkyl, especially lower alkyl, for example unsubstituted C_1–C_3 alkyl, hydroxyl, alkoxy, especially lower alkoxy such as methoxy or ethoxy, substituted or unsubstituted alcohol, and unsubstituted or substituted carboxyl, for example COOH or $COCH_3$. In other embodiments R_{7-18} can also be substituted or unsubstituted amino, and halogen.

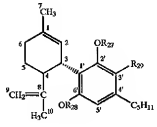
The cannabinoid has substantially no binding to the NMDAr (for example an IC_{50} greater than or equal to 5 μM or 10 μM), has substantially no psychoactive activity mediated by the cannabinoid receptor (for example an IC_{50} at the cannabinoid receptor of greater than or equal to 300 nM, for example greater than 1 μM and a K_i greater than 250 nM, especially 500–1000 nM, for example greater than 1000 nM), and antioxidant activity, as demonstratable by the Fenton reaction or cyclic voltametry.

In other particular embodiments, the cannabinoids are one of the following:

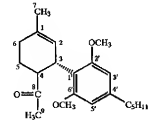


where R_{19} is substituted or unsubstituted alkyl, such as lower alkyl (for example methyl), lower alcohol (such as methyl alcohol) or carboxyl (such as carboxylic acid) and oxygen (as in =O); R_{20} is hydrogen or hydroxy; R_{21} is hydrogen, hydroxy, or methoxy; R_{22} is hydrogen or hydroxy; R_{23} is hydrogen or hydroxy; R_{24} is hydrogen or hydroxy; R_{25} is hydrogen or hydroxy; and R_{26} is substituted or unsubstituted alkyl (for example n-methyl alkyl), substituted or unsubstituted alcohol, or substituted or unsubstituted carboxy.

In yet other embodiments of the invention, the cannabinoids are

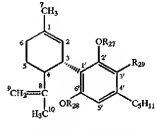


wherein numbering conventions for each of the ring positions are shown, and R_{27}, R_{28} and R_{29} are independently selected from the group consisting of H, unsubstituted lower alkyl such as CH_3, and carboxyl such as $COCH_3$. Particular examples of nonpsychoactive cannabinoids that fall within this definition are cannabidiol and



and other structural analogs of cannabidiol.

In more particular embodiments, the cannabinoid is used to prevent or treat an ischemic or neurodegenerative disease in the central nervous system of a subject, by administering to the subject a therapeutically effective amount of a cannabinoid to protect against oxidative injury to the central nervous system. The cannabinoid may be any of the compounds set forth above, or more specifically



wherein R_{27}, R_{28} and R_{29} are independently selected from the group consisting of H, lower alkyl such as CH_3, and carboxyl such as $COCH_3$, and particularly wherein

a) R_{27}=R_{28}=R_{29}=H

b) R_{27}=R_{29}=H; R_{28}=CH_3

c) R_{27}=R_{28}=CH_3; R_{29}=H

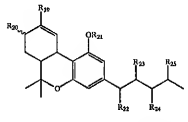
d) R_{27}=R_{28}=$COCH_3$; R_{29}=H

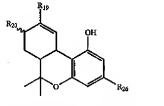
e) R_{27}=H; R_{28}=R_{29}=$COCH_3$

When R_{27}=R_{28}=R_{29}=H, then the compound is cannabidiol. When R_{27}=R_{29}=H and R_{28}=CH_3, the compound is CBD monomethyl ether. When R_{27}=R_{28}=CH_3 and R_{29}=H, the compound is CBD dimethyl ether. When R_{27}=R_{28}=$COCH_3$ and R_{29}=H, the compound is CBD diacetate. When R_{27}=H and R_{28}=R_{29}=$COCH_3$, the compound is CBD monoacetate. The ischemic or neurodegenerative disease may be, for

example, an ischemic infarct, Alzheimer's disease, Parkinson's disease, Down's syndrome, human immunodeficiency virus (HIV) dementia, myocardial infarction, or treatment and prevention of intraoperative or perioperative hypoxic insults that can leave persistent neurological deficits following open heart surgery requiring heart/lung bypass machines, such as coronary artery bypass grafts (CABG).

Of those 100 possible cannabinoid structures, Hampson elected to provide 68 different examples. Those 68 examples are as follows:

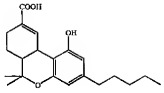


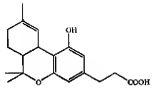


	Compound		R_{19}	R_{20}	R_{21}	R_{22}	R_{23}	R_{24}	R_{25}	R_{26}
H	5	7-OH-Δ^1-THC	CH_2OH	H	H	H	H	H	H	C_5H_{11}
H	6	6α-OH-Δ^1-THC	CH_3	α-OH						
H	7	6β-OH-Δ^1-THC	CH_3	β-OH						
	8	1'-OH-Δ^1-THC	CH_2			OH				
H	9	2'-OH-Δ^1-THC	CH_3				OH			
	10	3'-OH-Δ^1-THC	CH_3					OH		
	11	4'-OH Δ^1-THC	CH_3						OH	
H	12	6α,7-diOH-Δ^1-THC	CH_2OH	α-OH						
H	13	6α,7-diOH-Δ^1-THC	CH_2OH	β-OH						
	14	1',7-diOH-Δ^1-THC	CH_2OH			OH				
H	15	2',7-diOH-Δ^1-THC	CH_2OH				OH			
H	16	3',7-diOH-Δ^1-THC	CH_2OH					OH		
H	17	4',7-diOH-Δ^1-THC	CH_2OH						OH	
	18	1',β-diOH-Δ^1-THC	CH_2	β-OH		OH				
	19	1',3'-diOH-Δ^1-THC	CH_2			OH		OH		
	20	1',6α,7-triOH-Δ^1-THC	CH_2OH	α-OH		OH				
H	21	Δ^1-THC-6-one	CH_2	=O						
	22	Epoxyhexahydrocannabinol (HHTC)*	CH_2							
	23	7-oxo-Δ^1-THC	CHO							
H	24	Δ^1-THC-7"-oic acid	COOH							
H	25	Δ^1-THC-2"-oic acid	CH_2							C_2H_4COOH
H	26	1'-OH-Δ^1-THC-7"-oic acid	COOH			OH				
H	27	2'-OH-Δ^1-THC-7"-oic acid	COOH				OH			
H	28	3'-OH-Δ^1-THC-7"-oic acid	COOH					OH		
H	29	4'-OH-Δ^1-THC-7"-oic acid	COOH						OH	
H	30	3',4',5'-trinor-2'-OH-Δ^1-THC-7-oic acid	COOH							C_3H_6OH
H	31	7-OH-Δ^1-THC-2"-oic acid	CH_2OH							CH_2COOH
H	32	6β-OH-Δ^1-THC-2"-oic acid	CH_3	β-OH						CH_2COOH
H	33	7-OH-Δ^1-THC-2"-oic acid	CH_2OH							C_2H_4COOH
H	34	6β-OH-Δ^1-THC-3"-oic acid	CH_3	β-OH						C_2H_4COOH
H	35	6α-OH-Δ^1-THC-4"-oic acid	CH_3	α-OH						C_3H_6COOH
H	36	2',3'-dehydra-6U-OH-Δ^1-THC-4"-oic acid	CH_3	α-OH						C_3H_5COOH
H	37	Δ^1-THC-1',7-dioic acid	COOH							COOH
H	38	Δ^1-THC-2',7-dioic acid	COOH							CH_2COOH
H	39	Δ^1-THC-3',7-dioic acid	COOH							C_2H_4COOH
H	40	Δ^1-THC-4',7-dioic acid	COOH							C_3H_6COOH
H	41	1',2'-dehydro-Δ^1-THC-3',7-dioic acid	COOH							C_2H_3COOH
H	42	Δ^8-THC-glucuronic acid	CH_2	gluc†						
H	43	Δ^1-THC-7-oic acid glucuronide	COO	gluc†						

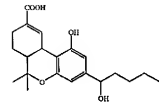
*Epoxy group in C-1 and C-2 positions
†Glucuronide
Note: R-group substituents are H if not indicated otherwise.

24

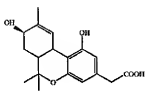




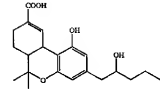
26



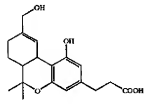
32



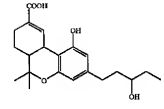
27



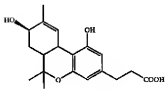
33



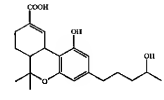
28



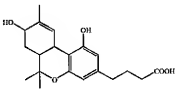
34



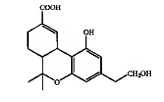
29



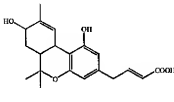
35



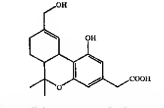
30



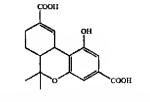
36



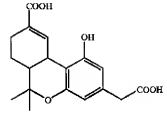
31



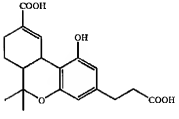
37



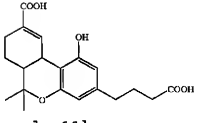
38



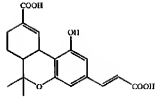
39



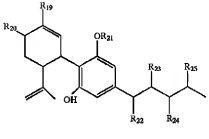
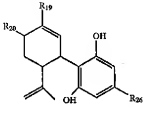
40



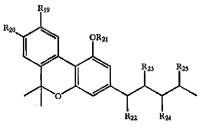
41



[Example 11]

Compound	R_{19}	R_{20}	R_{21}	R_{22}	R_{23}	R_{24}	R_{25}	R_{26}
								
44 CBD	CH_3	H	H	H	H	H	H	C_5H_{11}
45 7-OH—CBD	CH_2OH							
46 6α-	CH_3	α-OH						
47 6β-	CH_3	β-OH						
48 1'-	CH_3			OH				
49 2'-	CH_3				OH			
50 3'-	CH_3					OH		
51 4'-	CH_3						OH	
52 5'-	CH_3							$C_4H_9CH_2OH$
53 6,7-diOH—CBD	CH_2OH	OH						
54 3',7-diOH—CBD	CH_2OH					OH		
55 4',7-diOH—CBD	CH_2OH						OH	
56 CBD-7-oic acid	COOH							
57 CBD-3'-oic acid	CH_3							C_3H_6COOH

-continued

Compound	R_{19}	R_{20}	R_{21}	R_{22}	R_{23}	R_{24}	R_{25}	R_{26}
								
58 CBN	CH_3	H	H	H	H	H	H	C_5H_{11}
59 7-OH—CBN	CH_2OH							
60 1'-OH—CBN	CH_3			OH				
61 2'-OH—CBN	CH_3				OH			
62 3'-OH—CBN	CH_3					OH		
63 4'-OH—CBN	CH_3						OH	
64 5'-OH—CBN	CH_3							$C_4H_8CH_2OH$
65 2'-7-diOH—CBN	CH_2OH				OH			
66 CBN-7-oic acid	COOH							
67 CBN-1'-oic acid	CH_3							COOH
68 CBN-3'-oic acid	CH_3							C_3H_6COOH

Note: R-group substituents are H if not indicated otherwise.

From more than 100 possible cannabinoid structures and the 68 specific examples, Hampson did not disclose (1) the instant invention and (2) a small recognizable class of compounds with common properties in the totality of Hampson's disclosure as required by the *Petering* and *In re Ruschig* decisions. In fact, for twenty-five compounds (and there are more possible compounds) disclosed in Example 11 there were only a few in which R' is -COOH or CH_2OH. Of those few compounds having R' is -COOH or CH_2OH, the specific compounds are all different from the compounds of the invention. That merely confirms there was not a small recognizable class of compounds for the examiner to use its *Petering* logic, instead it confirms Hampson falls within the ambit of the *In re Ruschig* decision - the pending claims are allowable over Hampson et al.'s disclosure.

Still further, and importantly, Hampson does not describe the synthesis of even one single compound of Example 11. Merely describing a generic genus structure without providing how to synthesize the specific species structure is equivalent to admitting the specific species cannot be synthesized.

While Hampson mentions that the compounds can be in the form of racemate, or any of the single (+) and (-) enantiomers, it does not mention which compounds exist in which stereomeric configuraiotn. As well known, the separation of racemic mixture is a very complicated task.

Essentially, Hampson disclosed a genus broad enough to encompass the recited compound, yet Hampson failed to disclose a suggestion or motivation to select the claimed compounds that

fell within the broad genus without undue hind sight and without describing how to synthesize the claimed product or the generic genus.

The Examiner further refers to specific examples given at Col. 26 and Example 11 of Hampson.

Still further, the Examiner states that Hampson provides a specific example of a lower alkyl being 1,1,-dimethylheptyl (Col 11, lines 50-53).

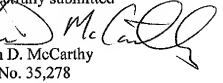
The Examiner further states that Hampson mentions that all compounds can include the (+) and (-) stereoisomers, as well as either the (+) or the (-) stereoisomers.

While Hampson mentions that the compounds can be in the form of racemate, or any of the single (+) and (-) enantiomers, Hampson does not mention which compounds exist in which stereomeric configuration. In addition Hampson ignores that the separation of racemic mixture is a very complicated task that cannot be merely disclosed in a slap dash manner. Hampson, therefore, fails to disclose the instant invention.

The Examiner's reference to Bisogno et al. (page 8 of the Action) has been noted. This publication is prior art discussed in the specification (first full paragraph of page 4 of the WO publication).

Therefore, it is respectfully submitted that claimed invention is patentable over Hampson et al. for the above-identified reasons. Accordingly, it is respectfully requested the examiner allow this application.

Respectfully submitted



Kevin D. McCarthy
Reg. No. 35,278

Roach, Brown, McCarthy & Gruber, P.C.
1920 Liberty Building - 424 Main Street
Buffalo, New York 14202